

REMARKS

I. Interview Summary

The Applicants' representative thanks Examiner Steele and SPE Paras for the courtesy and consideration shown during the interview of 19 July 2006. During that interview, the Applicants' representative discussed possible appeal, prior art including Ladner and Dower and their failure to teach or suggest certain elements of the claimed invention.

II. Patentability Arguments

A. The Rejection Under 35 U.S.C. §§ 102(a, e) or in the Alternative 103(a) Should Be Withdrawn

At page 5 of the office action, the Examiner newly rejected claims 44, 47-48 allegedly as being anticipated by Dower U.S. Patent No. 5,427,908 (Dower US) under 35 U.S.C. §102(e, a) or in the alternative § 103(a) reiterating that the claim element "providing a library of *in vitro* mutagenized nucleic acid from an existing antibody coding sequence" is a "product-by-process limitation." Applicants respectfully disagree with the Examiner's statement because the step of "providing a library of *in vitro* mutagenized nucleic acid from an existing antibody coding sequence..." is not a product-by-process limitation. Furthermore, because this step is not disclosed in Dower US, Dower US cannot anticipate the instant claims.

MPEP § 2131 provides that "[a] claim is anticipated only if each and every element as set forth in the claim is found, either expressly or inherently described in a single prior art reference." *Verdegaal Bros. v. Union Oil Co. of California*, 814 F.2d 628, 631, 2 USPQ2d 1051, 1053 (Fed. Cir. 1987). Furthermore, "[t]he identical invention must be shown in as complete detail as contained in the...claim. *Richardson v. Suzuki Motor Co.*, 868 F.2d 1226, 1236, 9 USPQ2d 1913, 1920 (Fed. Cir. 1989). Lastly, "the elements must be arranged as required by the

claim...” *In re Bond*, 910 F.2d 831, 15 USPQ2d 1566 (Fed. Cir. 1990). As discussed in detail below, Applicants submit that each and every element of the instant claims is not disclosed in Dower US.

At page 5 of the office action, the Examiner alleges, *inter alia*, that Dower US anticipates instant claims because it teaches filamentous bacteriophage library encoding antibody fragments which refers to the instant claimed binding domains of immunoglobulin. However, Applicants reiterate that Dower US is concerned with cloning of natural libraries and nowhere discloses the step of “providing a library of *in vitro* mutagenized nucleic acid from an existing antibody coding sequence.”

More specifically, Dower US refers to cloning genes from a nucleotide library, i.e., preparing a naturally diverse library then looking to clone a single protein that binds a particular ligand.

For example, Dower US states:

“The protein for which the DNA is enriched and cloned according to the present invention is typically an antibody or fragment thereof, but may also be any protein which may be cloned from a nucleotide library. In addition to antibodies, such proteins may include, for example, growth hormones, interferons, interleukins, hormones, enzymes, zymogens, etc. Proteins which may be cloned are those for which specific binding partners (e.g., antigen or hapten when the desired protein is an antibody) have been identified.”

In fact, on page 6 of the office action, the Examiner correctly states that “Dower does not teach that the library is prepared by *in vitro* mutagenized nucleic acid and from existing antibody coding sequences.”

In addressing that Applicants’ prior argument that Dower does not teach “providing a library of *in vitro* mutagenized nucleic acid from an existing antibody coding sequence...” the

Examiner again concludes that the required claim element is “still considered a product-by-process limitation...” a conclusion with which the Applicants respectfully disagree.

As discussed during the interview of 19 July 2006, the Applicants submit that the “providing a library of *in vitro* mutagenized nucleic acid from an existing antibody coding sequence” is an active step of providing a material, which is a nucleic acid library which has the physical characteristics of comprising antibody coding sequences which are mutants of a pre-existing antibody coding sequence created by *in vitro* mutagenesis. Because the claim limitation involves the step of providing a physical material of recited characteristics, Applicants submit it should be given full weight as a claim limitation when considering the patentability of the claims over Dower US, which does not teach a library having the recited characteristics.

In conclusion, because Dower US does not teach the step of providing a library of *in vitro* mutagenized nucleic acid from an existing antibody coding sequence, it cannot anticipate nor render obvious claims 44, 47-48 of the instant application.

It is well settled that in order to establish a *prima facie* case of obviousness, three basic criteria must be met. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine the reference teachings. Second, there must be a reasonable expectation of success. That is, the hypothetical person of ordinary skill in the art, at the time the invention was made, must have had a reasonable expectation that the proposed modification or combination would work to produce beneficial results. Finally, the references when combined must teach or suggest all the claim limitations. *See* MPEP § 2143. Because Dower US does not

teach or suggest all the claim limitations (e.g. the step of providing a library), no prima facie case of obviousness has been established.

For at least the foregoing reasons, rejection over Dower US under 35 U.S.C. §102 (a, e) or in the alternative 103(a) may be properly withdrawn.

B. The Rejections of Claims 44, 47-48 Under 35 U.S.C. §§ 102(a or e)

US Patent 5,837,500 to Ladner ("Ladner US") Should Be Withdrawn

At page 8 of the office action, the Examiner again rejected claims 44 and 47-48 allegedly as being anticipated by Ladner US Patent No. 5,837,500 under 35 U.S.C. § 102(e). Applicants respectfully traverse the rejections in view of the following remarks.

The Examiner characterizes Ladner US as disclosing a method of obtaining a nucleic acid encoding a proteinaceous binding domain that binds a predetermined target. On page 10 of the office action, the Examiner further alleges, *inter alia*, that "the member of specific binding pair members are the Fab antibody fragments which may read on the small fragments (under 40 amino acids) taught by Ladner of the instant claims." However, this assertion is in error because as stated in prior responses, Ladner US does not disclose display on filamentous bacteriophage multi-chain proteins such as Fab antibody fragments. Further, the Examiner's assertion that "Fab antibody fragments" may read on the small fragments (under 40 amino acids) taught by Ladner is incorrect. Fab antibody fragments are multi-chain proteins that are known in the art to be considerably larger than the 40 amino acid peptide described by Ladner as is explained by the 400 amino acid Fab disclosed in the present application.

Applicants enclose with this response page 32 of the *Penguin Dictionary of Biology*, (1994), along with bibliographic and title pages (cited on the attached PTO-SB-08b). The reference is listed on enclosed with this response PTO-SB-08B.

Figure 3 of the enclosed page 32 shows the nature of Fab fragments (shown on the right arm of the antibody molecule) and explains that as compared with a complete antibody they are as released by papain digestion. On the left arm the amino acid numbering is shown for the heavy and light chains starting with residue 1 at the N-terminus. The VL and CL regions together form 214 amino acids on this example, with the total VH and CH1 being of similar size. This is a representative number, but Fab fragments consist of two chains, wherein each chain is of the order of 210 amino acids in length (not exactly that number in each case).

Because Ladner US does not disclose display of multi-chain proteins, such as Fabs, the reference does not anticipate the present invention and therefore the rejection should be withdrawn.

On page 11 of the office action, the Examiner also states that the "antibody variable domain" of the referenced claims read on the instant claim "single chain antibody or scFv." However, as discussed herein and previously, the present claims do not claim scFv but rather Fab antibody fragments which are not disclosed by Ladner.

In conclusion, Ladner US cannot anticipate claims 44, 47-48 of the instant application because, *inter alia*, it does not disclose a method of obtaining a member of a specific binding pair wherein the specific binding pair member is a Fab fragment. Therefore, rejection over Ladner US under 35 U.S.C. §102(e) may be properly withdrawn.

C. Rejection over US patent application 2002/0150881 to Ladner, Now U.S. Patent No. 6,979,538, Under 35 U.S.C. § 102(a or e) Should Be Withdrawn

At page 10 of the office action, the Examiner reiterated that rejection of claims 44, 46-48, 51-52 allegedly as being anticipated by Ladner US application, now U.S. Patent No. 6,979,538, under 35 U.S.C. § 102(a or e). Applicants respectfully traverse this rejection in view of the following remarks.

At page 4 of the office action, the Examiner reiterates, *inter alia*, that the Ladner US anticipates the instant claims because “[T]he ‘antibody variable domain’ of the reference claims reads on the instant claim, or single chain antibodies or scFv because the reference teaches that the single chain antibody is a single chain polypeptide comprising binding two antigen regions....” However, as stated in Section II.B. above, the present claims are directed to a method of obtaining a member of a specific binding pair wherein the specific binding member is a Fab antibody fragment which is a multi-chain antibody fragment. Ladner does not disclose display on filamentous bacteriophage of a multi-chain polypeptide such as a Fab fragment of an antibody. As stated by the Examiner on page 11 of the office action “[T]he antibody variable domains of the reference claims read on the instant claim ‘single chain antibodies or scFv’ because the reference teaches that the single chain antibody is a single chain polypeptide comprising two antigen binding regions to fold together to bind an antigen...” [sic] Thus, they are, clearly by the Examiner’s own admission, not multi-chain Fab fragments of antibodies as presently claimed.

In conclusion, because Ladner US does not disclose display on filamentous bacteriophage of any multi-chain polypeptides such as Fab antibody fragments, the rejection of the instant claims over Ladner US under 35 U.S.C. §§102(a) or (e) maybe properly withdrawn.

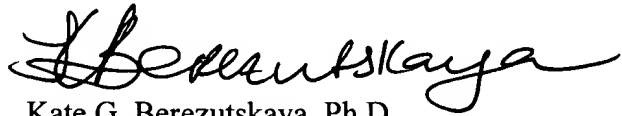
Conclusion

In view of the above amendments and remarks, applicants respectfully submit that the instant application is in good and proper order for allowance and early notification to this effect is solicited. If, in the opinion of the Examiner, a telephone conference would expedite prosecution of the instant application, the Examiner is encouraged to call the undersigned at the (312) 846-5622.

Respectfully submitted,

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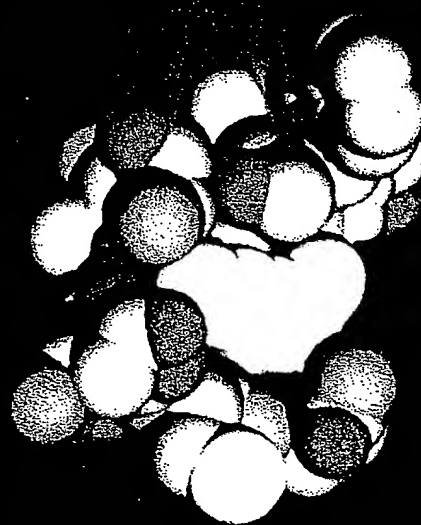
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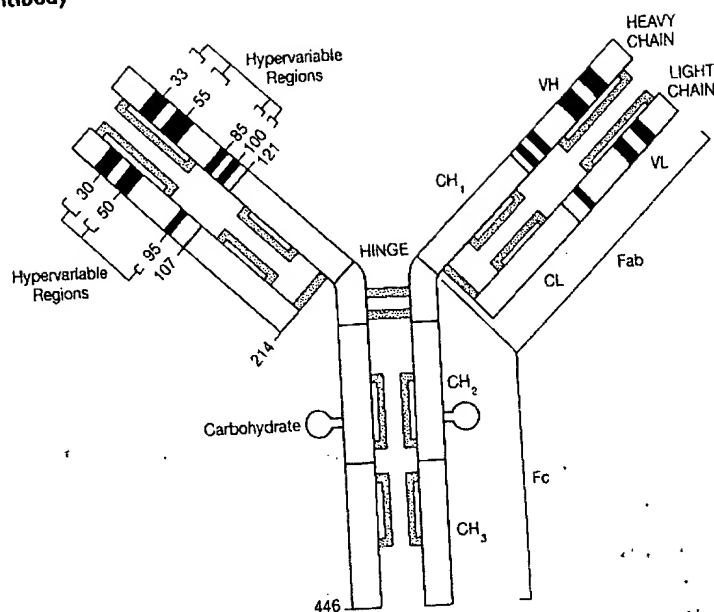


Fig. 3 Diagram of the basic IgG structure. The hypervariable regions (amino acid residues numbered) are the antigen-binding sites. Disulphide bridges are indicated within and between light and heavy by stippling. Fab regions are those released by papain digestion, along with the complement-fixing Fc portions, which also bind Fc receptors. See **antibody**.

the degree to which the molecule is a polymer of immunoglobulin 'monomers'. Each immunoglobulin unit comprises two identical H- (heavy) and two identical L- (light) polypeptide chains forming mirror images of each other and joined by a flexible hinge region involving disulphide bridges. They bind to antigen at specific antigen-binding regions provided uniquely by the combination of H- and L-chain amino-terminal portions (see Fig. 3), which are extremely variable in their amino acid sequences between different antibodies, in contrast to constant regions at their carboxy-terminal portions. Only about 20-30 amino acids of the variable re-

gions of H- and L-chains contribute to the antigen-binding site, these being located in three short hypervariable regions of each variable region. These lie themselves within relatively invariant 'framework regions' of the variable regions. The other biological properties of the molecule are determined by the constant domains of the heavy chains.

Digestion of antibody with papain produces two identical Fab (antigen-binding) fragments and one Fc (crystallizing) fragment. The latter region in the intact Ig (immunoglobulin) molecule is responsible for determining which component of the immune system the antibody will bind to (for Fc receptor, see **receptor**

(2)). The Fc region of IgG may bind phagocytes and the first component of **complement**. Only the IgG antibody can cross the mammalian placenta. IgM is the major Ig type secreted in a primary immune response, but IgG dominates in secondary immune responses (see **B cell**).

Transformation of B cells into differentiated antibody-producing plasma cells generally requires both antigen-presenting cells and a signal from a helper T cell (see **T cell**). Because B cells have only a few days' life in culture they are not suitable for commercial antibody production: however, if an antibody-producing B cell from an appropriately immunized mouse is fused to an appropriate mutant tumour B cell, the hybrid cell formed may continue dividing and producing the particular antibody required. The resulting **hybridoma** can be sub-cloned indefinitely, giving large amounts of antibody. Initial isolation of the appropriate B cell follows discovery of the required antibody in the growing medium. The purity of the resulting **monoclonal antibody** (mAb) and its production in response to what is possibly a minor component of an impure antigen mixture are both desirable features of the technique. All the **accessory molecules** known to participate in T cell recognition of their targets were first identified by monoclonal antibodies raised against these cell-surface markers. See **antibody diversity**, **antigen-antibody reaction**, **IgA-IgM**.

Antibody diversity (a. variation)

Production of different antibody molecules by different B cells (see Figs. 3 and 4 for symbols). Light and heavy